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TITLE: Use of relaxin in the treatment of bradycardia

Between 1974 and 1981, highly purified relaxin was isolated from the ovaries of pregnant pigs [Sherwood and O'Byrne Arch. Biochem. Biophys. 160, 185 (1974)], rats [Sherwood, O.D., Endocrinology 104, 886 (1979)], and sharks [Reinig et al., Endocrinology 109, 537 (1981)]. More recently, highly purified relaxin was isolated from the placentas of horses [Stewart, D. R. and Papkoff, Endocrinology 119, 1093 (1986)] and rabbits [Eldridge, R. K. and Fields, P. A., in Biology of Relaxin and its Pole in the Ruman M. Piccardi et al., Role in the Human M. Bigazzi et al., eds. 389-391, Excerpta Medica, Amsterdam (1983)]. Partially purified relaxin was obtained from cow and human corpora lutea (CL), placentas, and decidua. In the human, relaxin is known to exist in most abundance in the corpora lutea of pregnancy, however, relaxin has also been detected in non-pregnant female as well as in the male (seminal fluid) [Bryant-Greenwood, G. D., Endocrine Reviews 3, 62-90 (1982) and Weisse, G., Ann. Rev. Physiol. 46, 43-52 (1984)].

Recombinant techniques have first been applied to the isolation of cDNA clones for rat and porcine relaxins [Hudson et al., Nature 291, 127 (1981); Haley et al., DNA 1, 155 (1982)]. Two human gene forms have been identified by genomic cloning using probes from the porcine relaxin gene [Hudson et al., Nature 301, 628 (1983); Hudson et al., EMBO J. (issued Oct. 3, 1989)], although only one of these gene forms (termed H2) has been found to be transcribed in corpora lutea. It is unclear whether the other gene is expressed at another tissue site, or whether it represents a pseudo-gene. The fact that H2 relaxin is synthesized and expressed in the ovary suggests that this is the sequence that is directly involved in the physiology of pregnancy.

The structure of relaxin has apparently diverged considerably among species during Brief Summary Text (23): evolution. Only 40% to 48% amino acid sequence homology exists among porcine, rat, shark, and human relaxins.

H2 relaxin has been described to remodel the reproductive tract to facilitate birth process, including ripening of the cervix, thickening of the endometrium of the pregnant uterus as well as increased vascularization to this area, and an effect on collagen synthesis. H2 relaxin has also been associated with lactation, and some reports indicate that relaxin has a growth-promoting effect on mammary tissue [Wright, L. C. and Anderson, R. R., Adv. Exp. Med. Biol. 143, 341 (1982)].

It has been observed that in pregnant women heart rate increases by 2 weeks after conception, showing an elevation of about 7 beats/min, and continues to rise, obtaining elevations of about 10 beats/min by the 10th week [Clapp, J. F., Am. J. Obstet. Gynecol. 152,659-660 (1985)]. This change in early pregnancy is coincident with the first elevation of circulating relaxin in pregnant women [Stewart, D. R. et al., Supra].

Miller et al. [J. Pharmacol. Exp. Ther. 120, 426-427 (1957)] first reported that injection of an extract of pregnant sow ovary caused a transient fall in blood pressure when injected into anesthetized dogs. In contrast, injection of an extract of up to 50 .mu.g purified porcine relaxin in anesthetized rats did not affect blood pressure [Porter et al., J, Endocrinol. 83, 183-192 (1979)].

L Number	Hits	Search Text	DB	Time stamp
1	1269	(435/7.9).CCLS.	USPAT	2003/05/07 13:12
2	24	((435/7.9).CCLS.) and relaxin	USPAT	2003/05/07 13:13
3	8	(((435/7.9).CCLS.) and relaxin) and (mare or	USPAT	2003/05/07 13:29
		horse or burro or pony)		
4	0	((((435/7.9).CCLS.) and relaxin) and (mare	USPAT	2003/05/07 13:29
		or horse or burro or pony)) and toxicosis		
5	3	((((435/7.9).CCLS.) and relaxin) and (mare	USPAT	2003/05/07 13:30
		or horse or burro or pony)) and disease		

L Number	Hits	Search Text	DB	Time stamp
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3	8	(((435/7.9).CCLS.) and relaxin) and (mare or	USPAT	2003/05/07 13:29
		horse or burro or pony)		
4	0	((((435/7.9).CCLS.) and relaxin) and (mare	USPAT	2003/05/07 13:29
		or horse or burro or pony)) and toxicosis		
5	3	((((435/7.9).CCLS.) and relaxin) and (mare	USPAT	2003/05/07 13:32
		or horse or burro or pony)) and disease		
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8	1	(((435/7.72).CCLS.) and relaxin) and (horse	USPAT	2003/05/07 13:34
İ		or mare or pony)		
7	7	((435/7.72).CCLS.) and relaxin	USPAT	2003/05/07 13:36
9	4246	(435/7.1).CCLS.	USPAT	2003/05/07 13:36
10	23	((435/7.1).CCLS.) and relaxin	USPAT	2003/05/07 13:36
11	6	(((435/7.1).CCLS.) and relaxin) and (mare or	USPAT	2003/05/07 13:37
1		horses or pon\$3)		

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ļ		or horse or burro or pony)) and toxicosis		
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		or horse or burro or pony)) and disease		
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		or mare or pony)		
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		horses or pon\$3)		
12 .	223	kit and relaxin	USPAT	2003/05/07 13:45
13	70	(kit and relaxin) and (mare\$1 or horses or	USPAT	2003/05/07 13:46
		pon\$3)		
14	3	((kit and relaxin) and (mare\$1 or horses or	USPAT	2003/05/07 13:46
		pon\$3)) and (((435/7.1).CCLS.) and relaxin)		